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ORIGINAL RESEARCH

Coronary Artery Calcium and Cognitive Decline in the Diabetes Prevention Program Outcomes Study

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BACKGROUND: Our aim was to investigate the association of coronary artery calcium (CAC) with cognitive function in adults with impaired glucose tolerance or type 2 diabetes.

METHODS AND RESULTS: The Diabetes Prevention Program was a randomized controlled trial comparing an intensive lifestyle intervention, metformin, or placebo for prevention of type 2 diabetes among patients with prediabetes. After 3 years, intensive lifestyle intervention and placebo were stopped, the metformin arm was unmasked, and participants continued in the DPPOS (Diabetes Prevention Program Outcomes Study). Approximately 14 years after randomization (Y14), CAC (Agatston score) was assessed with computed tomography, and cognitive performance was assessed with the Spanish English Verbal Learning Test (SEVLT) and Digit Symbol Substitution Test. SEVLT and Digit Symbol Substitution Test were reassessed 5 years later (Y19) along with the Modified Mini-Mental State Exam. We examined cross-sectional and longitudinal associations between CAC and cognition among 1931 participants using linear and logistic regression. In unadjusted analyses, compared with no calcification, CAC score >300 was associated with decreased performance on all cognitive tests at Y14 in both sexes. Additionally, CAC >300 was associated with a greater 5-year decline in SEVLT Immediate Recall in both sexes and SEVLT Delayed Recall in women. After adjustment for demographic, genetic, metabolic, vascular, and behavioral covariates, CAC score >300 remained associated with greater decline in only SEVLT Delayed Recall in women.

CONCLUSIONS: In women with prediabetes or diabetes, CAC >300, compared with no calcification, was independently associated with greater decline in verbal memory.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT00038727.

Key Words: cognitive impairment ■ coronary artery calcium ■ diabetes ■ prediabetes ■ subclinical atherosclerosis

Coronary artery calcium (CAC) is a well-established surrogate measure of subclinical atherosclerotic cardiovascular disease (ASCVD).[1] Several population-based studies have suggested an association between CAC and cognitive impairment, especially decreased information-processing speed and increased risk of dementia.[2–4] While it is known that persons with prediabetes and type 2 diabetes (T2D) have higher

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CLINICAL PERSPECTIVE

What Is New?

- In this Diabetes Prevention Program Outcome Study sample of older adults with long-standing prediabetes or diabetes, we found that a high coronary artery calcium (CAC) score (>300), when compared with CAC absence, was associated with poorer performance on verbal learning and memory, and information-processing speed in both sexes.
- Additionally, CAC >300 was associated with greater declines in verbal learning in both sexes, and verbal memory in women, when cognitive testing was repeated 5 years later.
- Furthermore, after adjustment for several known risk factors for cognitive impairment and atherosclerotic cardiovascular disease, CAC >300 remained associated with greater decline in verbal memory in women.

What Are the Clinical Implications?

- CAC is associated with poorer cognition and cognitive decline; therefore, strategies aimed at prevention of atherosclerotic cardiovascular disease among the high-risk group of persons with prediabetes and type 2 diabetes might also be helpful in preventing cognitive decline.

Nonstandard Abbreviations and Acronyms

3MS	Modified Mini-Mental State examination
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcome Study
DSST	Digit Symbol Substitution Test
ILS	intensive lifestyle intervention
SEVLT	Spanish English verbal learning test
SEVLT-IR	Spanish English Verbal Learning Test—immediate recall
SEVLT-DR	Spanish English Verbal Learning Test—delayed recall
T2D	type 2 diabetes

CAC and increased risk of ASCVD,[5–7] there is a dearth of data on the relationship between CAC and cognitive function in this high-risk group.

The Diabetes Prevention Program (DPP) Outcomes Study (DPPOS) is a long-term follow-up of adults with overweight/obesity and impaired glucose tolerance (also known as prediabetes) who were initially randomized to an intensive lifestyle intervention (ILS), metformin, or placebo. A majority of DPPOS participants developed T2D during follow-up. A prior DPPOS investigation found that men had greater CAC accumulation than women, and both CAC presence and severity were lower in the metformin group versus placebo group in men,[8] while there were no differences in CAC between lifestyle and placebo groups in either sex. In the current DPPOS investigation, we examined cross-sectional and longitudinal associations between CAC and cognition, stratified by sex.

METHODS

The DPP and DPPOS data and materials have been made publicly available at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) repository and can be accessed at https://repository.niddk.nih.gov/studies/dppos/.

Design and Interventions

The design and methods of the DPP[9] and DPPOS[10] have been previously reported (ClinicalTrials.gov: NCT00004992 and NCT00038727). Briefly, in the DPP, during 1996 to 1999, a total of 3234 adults with overweight/obesity and impaired glucose tolerance were randomized to ILS, or masked metformin 850 mg or placebo twice daily. The masked treatment phase ended in 2001 after 2.8 years of average follow-up with the main finding that ILS and metformin led to 58% and 31% reductions, respectively, in the incidence of T2D compared with placebo.[9] Thereafter, placebo was discontinued, and unmasked metformin was provided to the group originally assigned to it. During long-term follow-up (DPPOS), for participants in the metformin group, when their hemoglobin A1c (HbA1c) levels reached 7% or higher, study-provided metformin was discontinued, and clinical care was transferred to their primary care physicians for management of diabetes; all other participants were referred to their primary care physicians when their diabetes was diagnosed. For all trial phases, written informed consent was obtained from all participants and studies were approved by each center's institutional review board. An independent data safety monitoring board appointed by the study sponsor (NIDDK) oversaw the studies.

Participants

At DPP entry, the participants were required to have a body mass index ≥24 kg/m^2 (≥22 kg/m^2 in Asian individuals), fasting plasma glucose level between 95 and 125 mg/dL, and impaired glucose tolerance (2-hour postload glucose of 140–199 mg/dL). They were excluded if taking medications known to alter glucose tolerance or if they had illnesses that could reduce their

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life expectancy or their ability to participate in the trial. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board. The participants had a mean age of 50.6 years at randomization. All active DPP participants were eligible to continue in DPPOS and a total of 2779 consented to participate.

After an average follow-up of 14 years post-DPP randomization (Y14), 2029 participants had CAC assessment, and 2232 underwent cognitive testing. Reasons for nonparticipation in the CAC substudy included death or loss to follow-up before Y14, refusal of consent, or ineligibility (presence of coronary stent, atrial fibrillation, body weight >350 lb, or pregnancy). After 5 years (Y19), 1853 participants had cognitive testing. In the current analyses, we included only the participants who had *both* CAC assessment and cognitive testing. A small number of participants only partially completed the set of tests administered during cognitive testing sessions. Figure S1 shows the sample sizes and assessments included in the current analyses.

Measures

Coronary Artery Calcium

Chest computed tomography was performed by certified technologists at each site using prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector system, acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode. Subjects were scanned twice, and the CAC measurement was calibrated against a phantom of known physical calcium concentration. A radiologist or cardiologist, blinded to participant characteristics and treatment assignment, read all computed tomography scans at the central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA). Discrepancies were reviewed, and agreement was obtained through consensus. For each scan, a total phantom-adjusted averaged Agatston score[11] was calculated, defined as the sum of calcium measures from the left main, left anterior descending, circumflex, and right coronary arteries.

Cognitive Assessments

All cognitive tests below were administered in English or Spanish, with higher scores indicative of better cognitive function.

Spanish English Verbal Learning Test

The Spanish English Verbal Learning Test (SEVLT) is a test of verbal learning and memory, consisting of 3 trials of immediate recall of 15 words, followed by a different set of 15 words (distractor list) to create interference, and a fourth trial of delayed recall of the original 15 words.[12] We used the total score (range 0–45) of the first 3 trials as the outcome representing immediate recall (SEVLT-IR), and the score of the fourth trial (range 0–15) after the distractor list as the outcome representing delayed recall (SEVLT-DR).[13]

Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) is a test of information-processing speed in which the participant matches numbers to symbols.[14] The score (range 0–93) is the total number of correct number–symbol matches achieved in 90 seconds. In addition to motor speed, DSST performance requires selective attention, perceptual organization, visuomotor coordination, the ability to filter out irrelevant information, and working memory.[15]

Modified Mini-Mental State Examination

The Modified Mini-Mental State examination (3MS) (score range 0–100) is a measure of global cognitive function that includes orientation, concentration, language, praxis, and immediate and delayed recall.[16] When used as a screening instrument, a score of <78 has been suggested to be indicative of clinically significant cognitive impairment or possible dementia.[17,18]

The SEVLT and the DSST were administered at Y14 and Y19, and the 3MS was performed at Y19 only.

Other Assessments

Incident T2D was determined by an annual oral glucose tolerance test and semi-annual fasting plasma glucose tests, and required confirmation by a second test.[9,10] All analytical measurements were performed at the DPPOS Central Biochemistry Laboratory (University of Washington, Seattle). Participants were classified as carriers defined as homozygous (ε4/ε4) or heterozygous (ε4/ε2, ε2/ε4, ε4/ε3, and ε3/ε4), and noncarriers (ε2/ε2, ε3/ε3, ε2/ε3, and ε3/ε2) of APOE-ε4. Beck Depression Inventory, second edition,[19] a 21-item self-reported questionnaire of depressive symptoms, was administered at yearly visits. Demographic characteristics (age, race and ethnicity, educational level) and current smoking status were self-reported. Concomitant medications (antihypertensive, lipid-lowering, and sedative/hypnotic medications) were self-reported. Antidiabetic medications were recorded by study dispensing records as well as self-report. Data for history of stroke and coronary artery disease were obtained via self-report and confirmed via review of hospital records. Body weight, body mass index, blood pressure, diabetes status, HbA1c, fasting plasma glucose, and serum lipid measures were assessed during the study visits. Physical activity was assessed with the Modifiable Activity Questionnaire.[20]

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Statistical Analysis

We present the characteristics of the study participants at Y14 as mean±SD (with the exception of median [Q1; Q3] for CAC score) for continuous variables, and the numbers and corresponding percentages for categorical variables, stratified by CAC severity, sex, and treatment groups. Comparisons between the groups were made by the Student *t* test or the ANOVA test for quantitative variables and the χ^2 test of independence for categorical variables. We list nominal *P* values with no adjustment for multiple comparisons. All tests are 2-sided, with $P < 0.05$ considered significant.

We analyzed CAC severity as a categorical variable applying the Agatston score cut points used in the Multi-Ethnic Study of Atherosclerosis[21]: 0 (absent), 1 to 100, 101 to 300, and >300 (4 categories) with CAC absence as the reference group. Because CAC load differed significantly between men and women, we examined their CAC associations separately.

We analyzed SEVLT-IR, SEVLT-DR, DSST, and 3MS total scores as continuous variables. We adjusted for baseline values of the cognitive test scores. Additionally, we examined 3MS as a categorical variable with a cut point score of <78, which was suggested to indicate clinically significant cognitive impairment.[17,18]

We included APOE-ε4 carrier status as a covariate because it is a strong risk factor for cognitive impairment.[22,23] During the DPPOS, some participants in the DPP-randomized placebo and ILS groups were treated with metformin for newly diagnosed diabetes, and some participants in the DPP-randomized metformin group discontinued the drug. To adjust for metformin treatment beyond its original DPP assignment, we constructed the variable *cumulative metformin exposure* in person-years of taking metformin.

Linear and logistic regression models stratified by sex were used to examine cross-sectional associations between CAC score and cognitive performance at Y14, and longitudinal associations with cognitive decline after 5 years. We utilized 2 models to adjust for covariates that are known to influence cognition, and a third model to adjust for vascular/metabolic risk factors and concomitant medications. All variables represent values at the time of cognitive testing.

Model 1: age, race and ethnicity, DPP-randomized treatment group.

Model 2: Model 1 *plus* APOE-ε4 (yes/no), education level (years), sedative/hypnotic medication use (yes/no), and depressive symptoms (Beck Depression Inventory, second edition total score).

Model 3: Model 2 *plus* cumulative metformin exposure, vascular/metabolic risk factors.

Vascular/metabolic risk factors included in Model 3 were as follows: current smoking status (yes/no), history of stroke (yes/no), history of clinical coronary artery disease (revascularization, unstable angina, and nonfatal myocardial infarction; yes/no), systolic blood pressure (mm Hg), body mass index (kg/m^2), physical activity (Modifiable Activity Questionnaire score), diabetes status (yes/no), HbA1c (%), fasting plasma glucose (mg/dL), total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), antihypertensive medications (yes/no), lipid-lowering medications (yes/no), and antidiabetic medications (yes/no).

To examine the effect of diabetes on cognitive performance, we examined least-squares means of the 5-year change in SEVLT-IR, SEVLT-DR, and DSST by CAC level, interacted with sex, age, and diabetes status. We adjusted the group least-squares means for race and ethnicity, DPP-randomized treatment group, APOE-ε4, education level, sedative/hypnotic medication use, depressive symptoms, and interaction between CAC category, and sex, age, and diabetes status.

Due to potential bias from missing cognitive data, we conducted sensitivity analyses to account for the 25% of participants with missing cognitive function value, 25% at Y19 and 10% at Y14, using multiple imputation models with 5 imputation runs using the mice package in R. The imputation model included the demographic covariates (Model 1 and 2) at Y14 and clinical covariates at Y14 and Y19, while the analytic model adjusted for Model 1, Model 2, and Model 3 as above, respectively.

RESULTS

Characteristics of the Overall Sample

Women represented 69% of the 2029 participants who had CAC assessment at Y14 (Table 1). The mean±SD age of the participants was 64.4±9.7 years at Y14 and 68.9±9.3 years at Y19, with 66% and 83% aged ≥60 years, respectively (Table S1). Among these participants, the prevalence of diabetes increased from 55% at Y14 to 64% at Y19. However, the average HbA1c of all participants was lower at Y19 than at Y14 (6.4% versus 6.6%; $P=0.006$), suggesting that their glycemia was well managed following diabetes diagnosis. Consistent with contemporary clinical management, their use of antihypertensive ($P=0.003$) and lipid-lowering medications ($P=0.012$) increased from 61% and 48% at Y14 to 67% and 53%, respectively, at Y19.

Characteristics of the Participants by Sex and Treatment Group

Women constituted ≈69% to 70% of the participants, and on the average, they were 3 to 4 years younger, had higher body mass index, lower physical activity level, lower education, higher depressive symptoms, and a smaller percentage were taking lipid-lowering medications compared with men (Table S1). Overall,

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Table 1. Sex-Stratified Characteristics According to CAC Score

Characteristic	Men						Women					
	All	0	1–100	101–300	>300	*P* value	All	0	1–100	101–300	>300	*P* value
Participants, n (%)	627	120 (19.1)	168 (26.8)	102 (16.3)	237 (37.8)		1402	696 (49.6)	423 (30.2)	165 (11.8)	118 (8.4)	
Age at visit, y, mean±SD	67.3±10	60.9±9.2	64.8±9.5	67.6±8.1	72.1±9.1	<0.001	63.1±9.2	59.9±8.4	64.2±8.6	68.1±7.8	70.1±9.4	<0.001
25 to <60 y, n (%)	144 (100)	57 (39.6)	49 (34)	13 (9)	25 (17.4)	<0.001	538 (100)	355 (66)	141 (26.2)	24 (4.5)	18 (3.3)	<0.001
≥60 y, n (%)	483 (100)	63 (13.1)	119 (24.6)	89 (18.4)	212 (43.9)		864 (100)	341 (39.5)	282 (32.6)	141 (16.3)	100 (11.6)	
Racial or ethnic group												
White, n (%)	354 (100)	47 (13.3)	83 (23.4)	66 (18.7)	158 (44.6)	<0.001	713 (100)	336 (47.1)	216 (30.3)	82 (11.5)	79 (11.1)	<0.001
Black, n (%)	102 (100)	27 (26.5)	31 (30.4)	17 (16.6)	27 (26.5)		320 (100)	164 (51.3)	102 (31.9)	35 (10.9)	19 (5.9)	
Hispanic, n (%)	101 (100)	33 (32.7)	35 (34.6)	10 (9.9)	23 (22.8)		225 (100)	103 (45.8)	80 (35.5)	31 (13.8)	11 (4.9)	
Asian, n (%)	58 (100)	9 (15.5)	15 (25.8)	8 (13.8)	26 (44.9)		43 (100)	23 (53.5)	12 (27.9)	4 (9.3)	4 (9.3)	
American Indian, n (%)	12 (100)	4 (33.3)	4 (33.3)	1 (8.4)	3 (25)		101 (100)	70 (69.3)	13 (12.9)	13 (12.9)	5 (4.9)	
DPP treatment assignment												
Placebo, n (%)	208 (33.2)	34 (28.3)	68 (40.5)	28 (27.5)	78 (32.9)	0.028	480 (34.2)	245 (35.2)	141 (33.1)	54 (32.7)	40 (33.9)	0.747
Metformin, n (%)	212 (33.8)	54 (45)	44 (26.2)	37 (36.3)	77 (32.5)		458 (32.7)	222 (31.9)	147 (34.8)	48 (29.1)	41 (34.7)	
Lifestyle, n (%)	207 (33)	32 (26.7)	56 (33.3)	37 (36.3)	82 (34.6)		464 (33.1)	229 (32.9)	135 (31.9)	63 (38.2)	37 (31.4)	
Cumulative metformin exposure, y, mean±SD	7.2±7.3	8.2±7.9	6.2±7	7.5±7.5	7.7±7.3	0.146	4.6±5.4	4.4±5.3	4.9±5.6	4.5±5.3	5.1±5.5	0.345
APOE-ε4*												
Positive, n (%)	148 (27.6)	30 (29.1)	40 (28)	22 (25.9)	56 (27.2)	0.965	299 (25.4)	136 (23.4)	96 (26)	32 (25.6)	35 (34.3)	0.135
Education, y, mean±SD	15.4±3.1	15.1±3.2	15.1±3.3	15.7±3.2	15.6±2.9	0.141	14.7±3.0	14.8±3.0	14.5±3.1	14.9±3.3	14.4±2.7	0.173
BDI-II, total score, mean±SD	3.7±4.3	3.8±4.8	3.4±4.2	3±3.9	4±4.2	0.257	4.9±5.1	4.8±5.1	5±5.4	4.5±4.6	5.4±4.7	0.490
BMI, kg/m^2, mean±SD	30.8±5.8	31.4±6	31.9±6.6	30.7±5.1	29.8±5.2	0.003	33.6±6.8	34.1±6.7	33.7±7	32.4±6.8	31.6±6.3	0.001
MAQ score, mean±SD	20.1±20.6	16.7±16.7	17.2±17.9	24.9±23.2	21.7±22.4	0.004	13±15.4	13.2±15.3	13.2±16.2	11.6±13.9	12.8±15.9	0.696
SBP, mm Hg, mean±SD	122±15	123±13	122±15	123±13	122±15	0.950	121±15	120±15	123±14	123±15	122±16	0.003
Diabetes diagnosis, n (%)	349 (55.7)	63 (52.5)	94 (56)	54 (52.9)	138 (58.2)	0.698	769 (54.9)	370 (53.2)	231 (54.6)	99 (60)	69 (58.5)	0.361
HbA1c, %, mean±SD	6.5±1.3	6.9±1.5	7±1.3	6.2±0.9	6.5±1.3	0.035	6.6±1.4	6.6±1.5	6.6±1.4	6.6±1.2	6.2±0.8	0.070
TC, mg/dl, mean±SD	163±30	161±39	195±14	144±13	158±27	0.192	196±31	197±24	199±37	211±54	180±32	0.550
HDL-C, mg/dl, mean±SD	50±15	48±12	56±15	44±13	51±19	0.830	57±12	61±9	53±14	47±20	62±13	0.118
Lipid-lowering med(s), yes, n (%)†	348 (55.5)	50 (41.7)	78 (46.4)	59 (57.8)	161 (67.9)	<0.001	621 (44.4)	255 (36.7)	196 (46.4)	88 (53.7)	82 (69.5)	<0.001
BP-lowering med(s), yes, n (%)†	394 (62.8)	67 (55.8)	101 (60.1)	63 (61.8)	163 (68.8)	0.083	845 (60.4)	356 (51.3)	279 (66.1)	118 (72)	92 (78)	<0.001
Antidiabetic med(s), yes, n (%)	233 (31.1)	32 (27.6)	53 (32.3)	26 (26.3)	80 (34.5)	0.379	475 (30.9)	202 (29.9)	117 (28.9)	64 (39.5)	38 (33.9)	0.067
Sedative/hypnotic use, yes, n (%)	20(2.8)	3(2.6)	5(3)	2(2)	6(2.6)	0.967	51 (3.3)	17 (2.5)	13 (3.2)	4(2.5)	7(6.2)	0.188

CAC was assessed only once during year 14. The participant characteristics represent their assessments at the time they had cognitive testing.

BDI-II indicates Beck Depression Inventory, version II; BMI, body mass index; BP, blood pressure; CAC, coronary artery calcium; DPP, Diabetes Prevention Program; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MAQ, Modifiable Activity Questionnaire to assess physical activity; SBP, systolic blood pressure; TC, total cholesterol.

*APOE-ε4 result was available for 1661 participants at year 14, and 1553 participants at year 19.

†Data for lipid-lowering and BP-lowering medications were available for all participants at year 14 and 1737 participants at year 19. *P* values represent the comparisons among the groups using the Student *t* test or the ANOVA test for quantitative variables and the χ^2 test of independence for categorical variables.

just over half of the participants were White race with a higher percentage of non-White participants among women, and there were no differences in race or ethnicity across treatment groups (Table S2). Approximately one-fourth of the participants were APOE-ε4 carriers, and their distribution was balanced across the sex and treatment groups (Tables S1 and S2).

Characteristics of the Participants by CAC Severity

Consistent with prior studies,[24,25] CAC load was higher among participants of older age, male sex, White race, and those taking antihypertensive and lipid-lowering medications (Table 1). All cognitive test scores decreased with increased CAC severity (Table S3).

Cognitive Performance by Age, Sex, and Treatment Group

Participants aged ≥60 years performed worse on most cognitive tests compared with those <60 years at both Y14 and Y19 (Table S4); additionally, participants aged ≥60 years at Y14 had greater decline in SEVLT-IR (men and women), SEVLT-DR (women only), and DSST (men

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and women) scores. Women performed significantly better than men on all cognitive tests at both Y14 and Y19 (Table S1). However, cognitive performance scores did not differ by randomized DPP group (Table S2). Among women, ILS group had statistically significant (P=0.04) lower mean SEVLT-DR score at Y14 and lower (P=0.03) mean 3MS score at Y19 (Table S5) compared with the metformin group.

Cognitive Performance by CAC Severity

Comparison of cognitive performance across CAC severity categories (Figure 1 and Table S3) showed that participants of both sexes in the CAC >300 category performed worse on all cognitive tests at Y14 and had greater declines at Y19, with the exception of mean 3MS scores in men only. Women with CAC score >300 had greater decline from Y14 to Y19 in mean SEVLT-DR scores than men (–1.9±3.0 versus –1.2±2.6; P=0.04; Figure 1 and Table S3). There were no significant differences by sex in the other CAC categories for changes over time in the mean scores of other cognitive tests.

Association of CAC Severity with Cognitive Performance

Table 2 shows the cross-sectional associations of CAC severity with cognitive performance measures at Y14 and the 3MS at Y19. In the unadjusted analyses, compared with CAC absence (CAC=0), all CAC levels (1–100, 101–300, and >300) were negatively associated with SEVLT-IR and DSST, and CAC >300 with SEVLT-DR in women. In men, CAC >300 was negatively associated with SEVLT-IR and SEVLT-DR, and CAC levels of 101–300 and >300 with DSST. None of these associations remained significant in the any of the adjusted models in both sexes.

Effect of Y14 CAC Severity on Longitudinal Change in Cognition

Table 3 shows the longitudinal associations between Y14 CAC severity and decline in SEVLT and DSST performance 5 years later. In women, in the unadjusted analyses, compared with CAC absence (CAC=0), CAC levels of 101 to 300 and >300 were associated with greater decline in SEVLT-IR and SEVLT-DR scores. Additionally in women, CAC >300 retained its association with greater decline in SEVLT-DR scores in all 3 adjusted analyses. In men, in the unadjusted analyses, CAC >300 was associated with a greater decline in SEVLT-IR, but not with changes in other cognitive test scores, and there were no significant associations in any of the adjusted analyses.

The above associations did not change in the sensitivity analyses with imputed data for all cognitive tests (Table S6).

As shown in Figure 2, among participants with CAC score >300, women had a greater decline in SEVLT DR than men; this decline was prominent among older women.

Effect of Diabetes on Longitudinal Change in Cognition

Men with CAC level of 100 to 300 had a greater decline in DSST score if they had diabetes versus no diabetes (Figure 2). In women with CAC level of >300, SEVLT-IR score increased over time if they had diabetes present versus absent.

Global Cognitive Performance Assessed with 3MS

The 3MS test was administered only at Y19. Mean 3MS score decreased with increasing CAC score in women

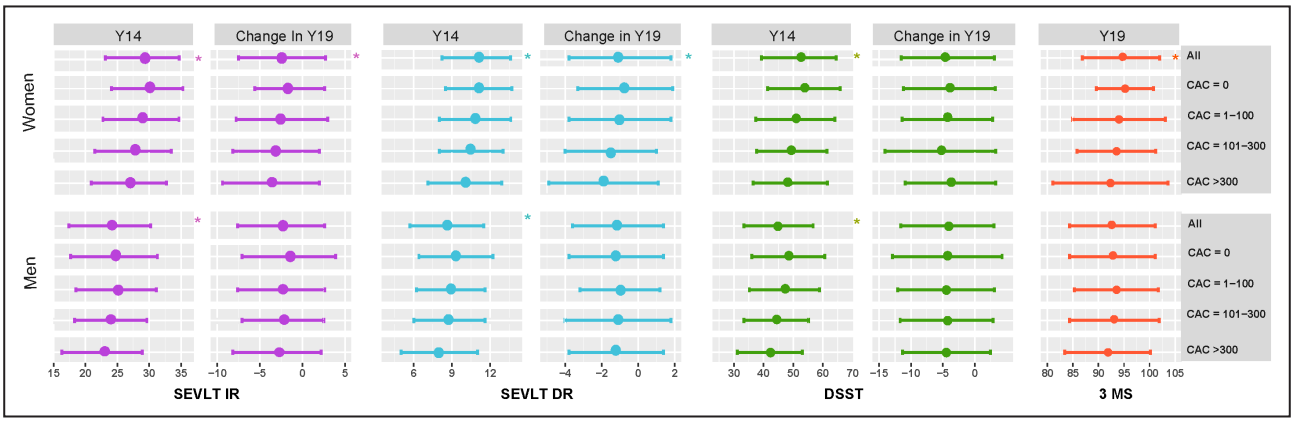

Figure 1. Cognitive function and 5-year decline by CAC severity, stratified by sex.
3MS indicates Modified Mini-Mental State; CAC, coronary artery calcium; DSST, digit symbol substitution test; SEVLT-DR, Spanish English Verbal Learning Test, Delayed Recall; and SEVLT-IR, Spanish English Verbal Learning Test, Immediate Recall. 3MS was administered at Year 19 only. *P<0.05.

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Table 2. Effects of CAC Severity (by Category) on Cognition, Stratified by Sex

	Men (β with 95% CI compared with CAC=0)				Women (β with 95% CI compared with CAC=0)			
	CAC=1–100	CAC=101–300	CAC>300	*P* value	CAC=1–100	CAC=101–300	CAC >300	*P* value
SEVLT, immediate recall Y14								
Model 0	0.15 (–1.37 to 1.67)	–0.54 (–2.25 to 1.17)	–1.98 (–3.41 to –0.56)*	<0.01†	–1.11 (–1.82 to –0.39)*	–2.15 (–3.15 to –1.15)*	–2.87 (–4.03 to –1.70)*	<0.01
Model 1	0.83 (–0.60 to 2.25)	0.63 (–1.02 to 2.27)	0.30 (–1.18 to 1.78)	0.53	–0.30 (–0.98 to 0.38)	–0.41 (–1.37 to 0.55)	–1.37 (–2.49 to –0.25)	0.15
Model 2	0.82 (–0.67 to 2.32)	0.11 (–1.61 to 1.82)	0.07 (–1.44 to 1.58)	0.63	–0.08 (–0.78 to 0.63)	–0.72 (–1.76 to 0.33)	–1.08 (–2.26 to 0.10)	0.20
Model 3	0.88 (–1.24 to 3.01)	1.10 (–1.35 to 3.57)	0.26 (–1.78 to 2.30)	0.50	–0.11 (–1.08 to 0.868)	–0.56 (–1.91 to 0.79)	–1.24 (–2.84 to 0.37)	0.26
SEVLT, delayed recall Y14								
Model 0	–0.51 (–1.21 to 0.19)	–0.58 (–1.37 to 0.21)	–1.38 (–2.04 to –0.73)*	<0.01†	–0.32 (–0.65 to 0.01)	–0.60 (–1.07 to –0.13)*	–1.08 (–1.63 to –0.54)*	<0.01
Model 1	–0.24 (–0.91 to 0.43)	–0.13 (–0.90 to 0.64)	–0.51 (–1.20 to 0.19)	0.40	0.04 (–0.28 to 0.36)	0.17 (–0.28 to 0.62)	–0.39 (–0.92 to 0.14)	0.27
Model 2	–0.20 (–0.91 to 0.51)	–0.20 (–1.00 to 0.61)	–0.50 (–1.21 to 0.22)	0.24	0.06 (–0.27 to 0.39)	–0.06 (–0.54 to 0.43)	–0.37 (–0.93 to 0.18)	0.41
Model 3	0.18 (–0.81 to 1.19)	0.20 (–0.95 to 1.36)	–0.09 (–1.04 to 0.87)	0.50	–0.22 (–0.67 to 0.24)	–0.14 (–0.78 to 0.49)	–0.39 (–1.13 to 0.36)	0.26
DSST Y14								
Model 0	–1.27 (–4.03 to 1.49)	–3.76 (–6.86 to –0.66)*	–6.09 (–8.68 to –3.51)*	<0.01†	–3.01 (–4.58 to –1.44)*	–4.05 (–6.22 to –1.87)*	–4.55 (–7.10 to –2.01)*	<0.01†
Model 1	0.06 (–2.38 to 2.50)	–1.30 (–4.11 to 1.51)	–1.43 (–3.97 to 1.10)	0.52	–0.04 (–1.42 to 1.33)	1.77 (–0.16 to 3.70)	0.95 (–1.32 to 3.22)	0.39
Model 2	–0.85 (–3.34 to 1.64)	–2.18 (–5.02 to 0.68)	–2.39 (–4.91 to 0.14)	0.57	0.14 (–1.26 to 1.54)	1.15 (–0.92 to 3.22)	1.84 (–0.50 to 4.19)	0.41
Model 3	0.09 (–3.32 to 3.51)	–2.35 (–6.31 to 1.60)	–1.43 (–4.70 to 1.85)	0.50	0.05 (–1.84 to 1.93)	2.2 (–0.44 to 4.84)	2.01 (–1.09 to 5.12)	0.68
3MS Y19								
Model 0	0.84 (–1.26 to 2.94)	0.43 (–1.94 to 2.80)	–0.90 (–2.92 to 1.11)	0.31	–1.14 (–2.13 to –0.14)*	–1.71 (–3.15 to –0.26)*	–3.02 (–4.72 to –1.32)*	<0.01*,†
Model 1	1.39 (–0.61 to 3.39)	1.23 (–1.09 to 3.55)	0.71 (–1.39 to 2.81)	0.54	–0.06 (–0.98 to 0.87)	0.88 (–0.48 to 2.24)	–1.04 (–2.64 to 0.55)	0.24
Model 2	2.05 (–0.04 to 4.14)	2.22 (–0.24 to 4.69)	1.54 (–0.65 to 3.74)	0.22	0.04 (–0.93 to 1.00)	0.98 (–0.49 to 2.44)	–0.08 (–1.77 to 1.61)	0.59
Model 3	1.72 (–0.34 to 3.78)	2.02 (–0.44 to 4.48)	1.80 (–0.33 to 3.95)	0.28	–0.13 (–1.10 to 0.84)	0.91 (–0.53 to 2.35)	0.28 (–1.42 to 1.97)	0.56

Coronary artery calcium (CAC) is expressed as Agatston scores. 3MS test was administered at year 19 only, and 1670 participants had the assessment.

CAC indicates coronary artery calcium; SEVLT, Spanish English Verbal Learning Test; DSST, Digit Symbol Substitution Test; 3MS, Modified Mini-Mental State. Model 0: unadjusted; Model 1: age + race or ethnicity + Diabetes Prevention Program. Randomization Arm; Model 2: Model 1 + APOE-ε4 status + education + depressive symptom; Model 3: fully adjusted: Model 2 + cumulative metformin exposure (y) + vascular and metabolic risk factors (current smoking history, systolic blood pressure, body mass index, physical activity [Modifiable Activity Questionnaire score], diabetes status [yes/no], hemoglobin A1c, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, blood-pressure-lowering medications [yes/no], lipid-lowering medications [yes/no], and antidiabetic medications [yes/no], history of stroke [yes/no], history of clinical CAC [yes/no], and sedative/hypnotic use [yes/no]).

*Indicates significant difference vs the reference group in CAC=0 level ($P<0.05$) from the linear regression analyses.

†*P* values indicate an overall test of the difference among 4 CAC categories from the ANOVA for linear model fit in R.

but not in men (Table S3). Using a 3MS cut point score of <78, a greater percentage of women in the ≥60 years age group had clinically significant cognitive impairment at Y19 compared with women <60 years (4.1% versus 1.2%; $P=0.038$; Table S4); this difference by age group was not observed among men (Table S4).

DISCUSSION

ASCVD is associated with increased risk for dementia.[26–29] Diabetes, an independent risk factor for ASCVD, is also associated with cognitive decline.[22,23,30,31] Additionally, ASCVD and dementia share numerous other risk factors including older age, hypertension, hyperlipidemia, smoking, sedentary lifestyle, and inflammation.[32]

In this DPPOS cohort of adults with diabetes or prediabetes, who are a high-risk group for cognitive impairment, with a mean age of ≈64 years, we found that CAC level >300, when compared with CAC absence, was associated with poorer performance on verbal learning and memory (SEVLT-IR and SEVLT-DR) and information-processing speed (DSST) in both sexes in unadjusted analyses. Additionally, CAC >300 was associated with greater declines in verbal learning (SEVLT-IR) in both sexes, and verbal memory (SEVLT-DR) in women, when cognitive testing was repeated 5 years later. Furthermore, after adjustment in 3 models for known risk factors for cognitive impairment and ASCVD, CAC >300 remained associated with greater decline in SEVLT-DR scores in women, suggesting that CAC might be an independent risk factor for decline in verbal memory but not learning. Except for SEVLT-DR in women, the associations between CAC and cognitive performance were no longer significant after adjustment for demographic variables (Model 1), which indicated differences in these factors across the 3 CAC severity groups.

Our findings confirm the observations in several population-based studies that CAC is associated with cognitive impairment, although there are differences regarding which cognitive domain is affected by CAC and which subgroups of persons are affected.

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Table 3. Effects of CAC Severity on Cognitive Decline at Year 19, Stratified by Sex

	Men (β with 95% CI compared with CAC=0)				Women (β with 95% CI compared with CAC=0)			
	CAC=1–100	CAC=101–300	CAC >300	*P* value	CAC=1–100	CAC=101–300	CAC >300	*P* value
SEVLT, immediate recall								
Model 0	−0.77 (−2.10 to 0.56)	−0.70 (−2.21 to 0.80)	−1.40 (−2.67 to −0.14)*	0.19	−0.45 (−1.12 to 0.22)	−1.14 (−2.11 to −0.17)*	−1.71 (−2.86 to 0.56)*	<0.01†
Model 1	−0.03 (−1.22 to 1.15)	0.25 (−1.12 to 1.63)	−0.38 (−1.61 to 0.86)	0.98	−0.13 (−0.76 to 0.50)	−0.59 (−1.52 to 0.33)	−1.36 (−2.45 to −0.27)	0.44
Model 2	−0.05 (−1.20 to 1.30)	−0.16 (−1.62 to 1.29)	−0.12 (−1.40 to 1.15)	0.98	−0.18 (−0.86 to 0.49)	−0.19 (−1.21 to 0.82)	−0.93 (−2.11 to 0.24)	0.85
Model 3	−0.81 (−2.46 to 0.85)	−0.96 (−2.93 to 1.00)	−0.73 (−2.42 to 0.95)	0.19	−0.21 (−1.11 to 0.69)	0.46 (−0.83 to 1.75)	−0.06 (−1.55 to 1.43)	0.62
SEVLT, delayed recall								
Model 0	0.13 (−0.52 to 0.78)	0.03 (−0.71 to 0.76)	−0.003 (−0.62 to 0.62)	0.97	−0.21 (−0.57 to 0.15)	−0.77 (−1.28 to −0.25)*	−1.20 (−1.81 to −0.59)*	<0.01†
Model 1	0.26 (−0.34 to 0.86)	0.30 (−0.41 to 0.99)	0.22 (−0.42 to 0.85)	0.87	0.01 (−0.33 to 0.35)	−0.36 (−0.86 to 0.13)	−0.88 (−1.47 to −0.30)*	<0.01†
Model 2	0.29 (−0.37 to 0.95)	0.05 (−0.72 to 0.82)	0.23 (−0.45 to 0.90)	0.80	−0.04 (−0.40 to 0.32)	−0.29 (−0.83 to 0.25)	−0.99 (−1.62 to −0.36)*	0.03†
Model 3	0.27 (−0.63 to 1.17)	−0.07 (−1.14 to 0.99)	0.35 (−0.56 to 1.27)	0.74	0.22 (−0.25 to 0.69)	−0.23 (−0.92 to 0.45)	−1.09 (−1.87 to −0.31)*	<0.01†
DSST								
Model 0	−0.19 (−2.11 to 1.73)	−0.14 (−2.33 to 2.04)	−0.16 (−1.99 to 1.68)	0.99	−0.29 (−1.28 to 0.70)	−1.39 (−2.80 to 0.02)	0.17 (−1.52 to 1.87)	0.25
Model 1	−0.23 (−2.49 to 1.50)	−1.01 (−1.23 to 2.94)	−1.12 (−1.05 to 2.69)	0.58	−0.13 (−1.06 to 0.08)	−0.64 (−2.00 to 0.71)	0.87 (−0.74 to 2.49)	0.30
Model 2	−0.49 (−2.38 to 1.81)	−0.78 (−2.84 to 2.07)	−0.21 (−1.79 to 2.48)	0.81	−0.20 (−1.20 to 0.94)	−0.72 (−2.65 to 0.56)	0.78 (−1.56 to 2.18)	0.57
Model 3	0.13 (−2.64 to 3.11)	−3.33 (−6.60 to −0.02)*	−0.29 (−3.11 to 2.52)	0.048†	−0.02 (−1.43 to 1.39)	−0.24 (−2.29 to 1.82)	2.21 (−0.14 to 4.56)	0.39

Model 0: unadjusted; Model 1: age + race or ethnicity + Diabetes Prevention Program Randomization Arm; Model 2: Model 1 + APOE-ε4 status + education + depressive symptom; Model 3 fully adjusted: Model 2 + score of cognitive function at year 14 + cumulative metformin exposure (y) + vascular and metabolic risk factors (current smoking history, systolic blood pressure, body mass index, physical activity [Modifiable Activity Questionnaire score], diabetes status [yes/no], hemoglobin A1c, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, blood-pressure-lowering medications [yes/no], lipid-lowering medications [yes/no], and antidiabetic medications [yes/no], history of stroke [yes/no], history of clinical CAC [yes/no], and sedative/hypnotic use [yes/no]). Coronary artery calcium (CAC) is expressed as Agatston scores. The 3MS test was administered at year 19 only, and 1670 participants had the assessment.

3MS indicates Modified Mini-Mental State; CAC, coronary artery calcium; DSST, Digit Symbol Substitution Test; and SEVLT, Spanish English Verbal Learning Test.

*Indicates significant difference vs the reference group in CAC=0 level ($P<0.05$) from the linear regression analyses.

†*P* values indicate an overall test of the difference among 4 CAC categories from the ANOVA for linear model fit in R.

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In the Age, Gene, Environment Susceptibility (AGES)-Reykjavik Study, an analysis of cross-sectional data of 4250 older Icelandic subjects with an average age of 76 years showed that higher CAC score was associated with decreased information-processing speed and executive function, and increased risk of dementia.[2] The Rotterdam Study found that, among 2414 Dutch subjects with an average age of 69 years, larger CAC volumes were associated with lower executive function, information-processing speed, and motor speed.[3] In the Multi-Ethnic Study of Atherosclerosis study, among 6293 participants aged 45 to 84 years, who were free of cardiovascular disease and noticeable cognitive deficits at baseline, there were 271 dementia cases during a median follow-up of 12 years.[4] Higher baseline CAC score had a positive association with dementia risk, independent of vascular risk factors, stroke, and APOE-ε4. Similar to our study, in a recent community-based study of 1332 people aged 40 to 80 years in Beijing, China, CAC was associated with lower scores on verbal memory, but not the other domains of cognition.[33]

While our finding of higher CAC load among men is consistent with prior studies,[24,25] the surprising finding was the significant association between CAC and decline in mean SEVLT-DR score in women, which remained significant in fully adjusted models. This finding might imply that cognitive processes might be more vulnerable to the detrimental effects of the vascular processes associated with CAC in women. Alternatively, there might be a greater heterogeneity of CAC load in women, or that the effects of CAC on cognition are mediated via other causal pathways. While CAC is more prevalent in men, there is some evidence suggesting that CAC might be associated with greater risks in women. In a study of subjects 80+ years of age, CAC score of >400, compared with CAC score of 0, was associated with ≈3 times higher risk of dementia in White women only after 10+ years.[34] Furthermore, CAC presence was found to be associated with increased risk of ASCVD among women at low ASCVD risk in a meta-analysis of 5 large population-based cohorts,[35] and the addition of carotid intima-media thickness, another noninvasive measure of atherosclerosis, to Framingham risk factors improved the prediction of coronary heart disease and stroke in women, but not in men, in the Rotterdam Study.[36] Thus, there is some prior evidence suggesting that the presence of atherosclerosis might be associated with different levels of risks for women and men with regard to cardiovascular events and cognitive decline.

To our knowledge, our study is the first to examine the relationship between CAC and cognition among subjects

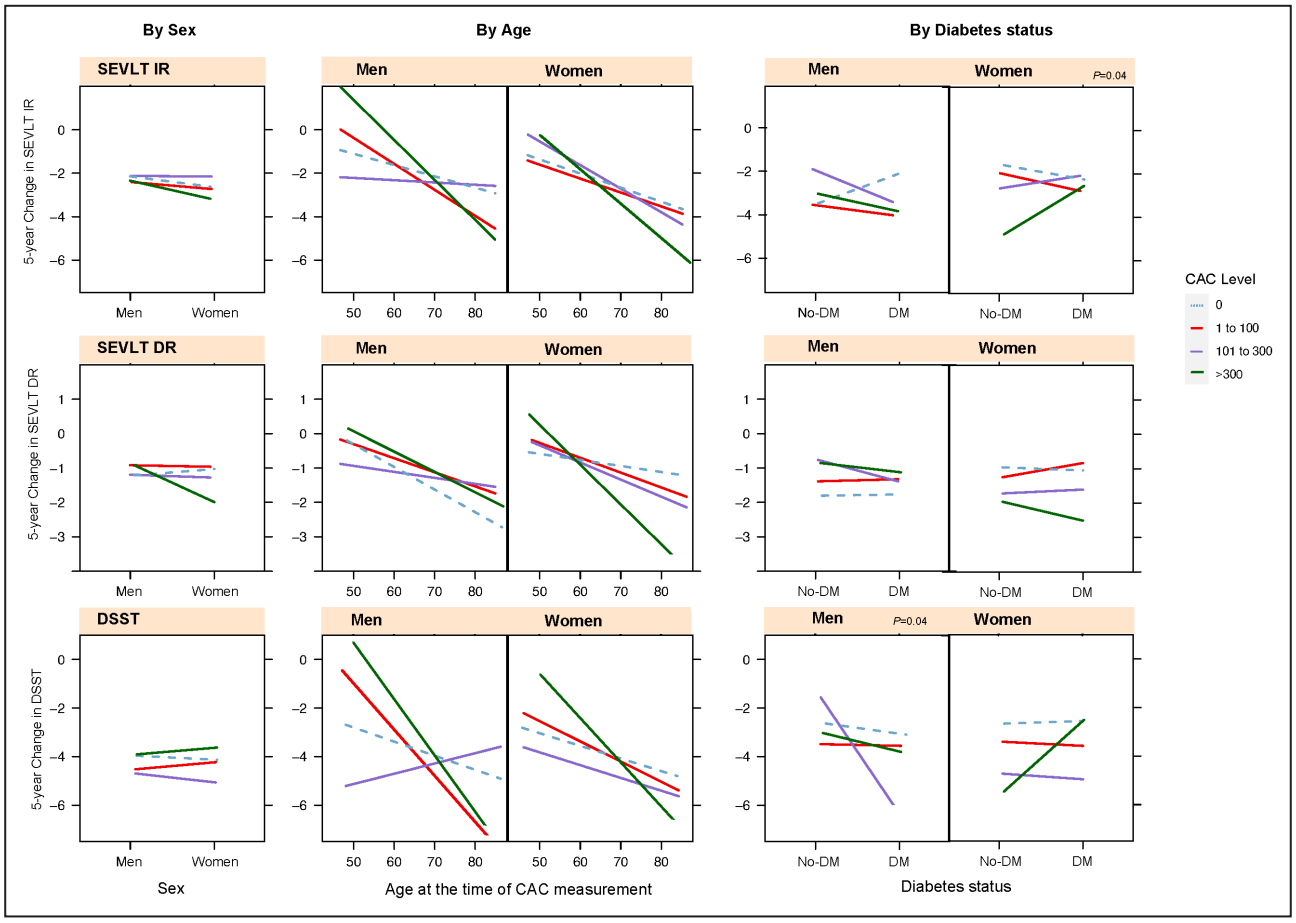

Figure 2. Adjusted mean change in cognitive function according to CAC level groups, stratified by sex, age, and diabetes status.

CAC indicates coronary artery calcium; DM, diabetes mellitus; DSST, Digit Symbol Substitution Test; SEVLT-DR, Spanish English Verbal Learning Test, Delayed Recall; and SEVLT-IR, Spanish English Verbal Learning Test, Immediate Recall. Shown are least-square means of cognitive test scores, adjusted for age, race and ethnicity, Diabetes Prevention Program randomization arm, APOE-ε4 status, education level, depressive symptoms, and interaction between CAC category, and sex, age, and diabetes status. The test for interaction that evaluated whether the association between CAC and cognitive function differed by sex, age, or diabetes status showed significant differences by age and diabetes for women.

with prediabetes and diabetes, who are a high-risk group for cognitive impairment. The strength of our study is a well-phenotyped sample of adults with long-standing diabetes or prediabetes; the availability of data for numerous demographic, vascular, metabolic, and behavioral assessments; and extensive sensitivity analyses.

Our findings are mostly consistent with population-based studies that found that CAC is associated with worse performance on cognitive tests, both cross-sectionally,[2,3] and longitudinally.[4,37] While prior studies observed that CAC was associated with poorer information-processing speed, we did not find an association between CAC and DSST performance. This is surprising because the DSST performance is thought to be closely linked to vascular cognitive impairment, and would have been expected to be associated with coronary disease burden measured with CAC.

In our study, the presence of diabetes did not consistently modify the association between CAC and cognition both in women and men. Effective clinical management of diabetes as reflected by mean HbA1c of 6.6% and 6.4% at Y14 and Y19, respectively, and increased use of proven cardioprotective therapies (ie, antihypertensive and lipid-lowering medications) during DPPOS might have reduced our ability to detect any potential detrimental effects of diabetes on cognition. Of note, recent DPPOS publications reported no significant differences by diabetes status in major adverse cardiovascular events[38] or mortality.[39]

Our finding that higher CAC was related to worse verbal learning performance in women but not in men deserves further discussion. Whether women have a higher risk of cognitive impairment than men is controversial. Some studies suggest that women have a higher burden of neurodegenerative disorders such as Alzheimer disease compared with men, which is characterized clinically by worse memory.[40–43] Furthermore, the heart disease advantage that

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women have compared with men is blunted in persons with T2D.[44] Although women performed better overall in verbal learning than men in this cohort, it is possible that they are more susceptible than men to the burden of vascular disease represented by CAC, or factors beyond sex hormones.[45] Unfortunately, we do not have brain imaging data to assess the relation of CAC with cerebrovascular and neurodegenerative disease.

Our study has some limitations. First, no formal cognitive assessments were performed when the participants entered the DPP. We assumed that the study participants, with a mean age of 50.6 years, had normal cognition at DPP entry based on medical history, physical examinations, and their consenting ability. Randomization group was not associated with cognitive performance 14 years after randomization.[46] Thus, it seems unlikely that cognition varied by treatment group at baseline. Moreover, the metabolic variables and risk factors were generally similar across the treatment groups and by sex. Second, the cognitive tests administered in the current study were limited and did not cover all domains of cognition. Third, CAC testing was performed only once at Y14, which meant the effects of CAC progression on cognition could not be ascertained. However, CAC is a measure of cumulative coronary disease burden. CAC does not regress over time and generally increases by 20% to 25% per year.[47] A greater progression of CAC was found to be associated with clinically relevant cognitive impairment in middle-aged individuals with childhood-onset type 1 diabetes.[48] Fourth, the association between CAC and change in global cognition could not be assessed because the 3MS test was administered only once at Y19. Fifth, we did not perform diagnostic assessments for clinical cognitive syndromes (eg, dementia, mild cognitive impairment), and cannot report on these outcomes. Sixth, other covariates and risk factors we did not include in our regression models could also have influenced the association between CAC and cognitive performance. Finally, selection bias might have resulted if those with severe CAC and worse cognitive performance were more likely to have missed assessments and were not included in the present analyses.

CONCLUSIONS

In conclusion, our study in a large sample of aging men and women with long-standing diabetes or prediabetes adds further support to the prior findings that coronary calcium is associated with poorer cognition and cognitive decline. Therefore, strategies aimed at prevention of ASCVD among the high-risk group of persons with prediabetes and T2D might also be helpful in preventing cognitive decline.

ARTICLE INFORMATION

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Disclosures

None.

Author Contributions

Gadde: study concept and design, data collection, writing, interpretation, supervision; Yin: analysis, writing, interpretation; Goldberg: study concept

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and design, data collection, writing, interpretation; Orchard: writing, interpretation; Schlögl: writing, interpretation; Dabelea: data collection, writing, interpretation; Ibebuogu: writing, interpretation; Watson: data collection, writing, interpretation; Pi-Sunyer: data collection, writing, interpretation; Crandall: data collection, writing, interpretation; Temprosa: study concept and design, analysis, writing, interpretation, supervision; Luchsinger: study concept and design, writing, interpretation, supervision.

Supplemental Material

Data S1
Tables S1–S6
Figure S1

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